REMARKS

Status of Claims

Claim 3 has been canceled; claims 5-8 and 12 have been withdrawn from consideration.

Claim 1 has been amended, without prejudice, to advance prosecution. Claims 13-17 have been added. Support for the amendments to claim 1 and new claims 13-17 can be found throughout the specification, including paragraphs [0007], [0044]-[0049]; [0065]-[0066], [0070-[0082], [0121], [0137], [0138] and [147]. No new matter has been added.

Claims 1, 2, 4, and 13-19 currently are pending. Applicants have submitted an RCE with this Response and respectfully request that the present amendment be entered.

Applicants respectfully request favorable consideration of the pending claims.

IDS

Applicants thank the Examiner for acknowledging receipt and consideration of the references in the Information Disclosure Statement submitted 9/21/09.

Claim Rejections

35 U.S.C. 101 rejection

The Examiner acknowledged that the rejection of claims 9-11 under 35 U.S.C. 101 had been rendered moot as these claims have been canceled.

35 U.S.C. 112 second paragraph rejection

The Examiner acknowledged that the rejection of claims 9-11 under 35 U.S.C. 112, second paragraph had been rendered moot as these claims have been canceled.

35 U.S.C. 112, first paragraph, enablement rejection

The Examiner maintained the rejection of claims 1-4 for reasons of record.

The Office action of March 19, 2009

The record shows that in the Office action of March 19, 2009, the Examiner had contended that the specification, while enabling for a method of decreasing A375 melanoma cell proliferation in vitro using a siRNA targeted to a gene encoding PRAME wherein the cells were cultured with a HDACi inhibitor PXD101 does not reasonably provide enablement for a method of treating a tumor in a subject comprising administering any inhibitor of PRAME, namely a siRNA in combination with any inhibitor of HDACi, namely N-hydroxy-3-(3-phenylsulfamoyl-phenyl-) acrylamide.

The Examiner however contended that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner considered the Wands factors in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

As for the breadth of the claims, the Examiner contended that the claims are drawn to a method of treatment of a tumor which comprises administering to a subject an inhibitor of PRAME in combination with an inhibitor of HDACi, wherein the inhibitor of PRAME is an siRNA and the inhibitor of HDACi is N¬hydroxy-3(3-phenysulfamoyl-phenyl-)acrylamide.

As for the nature of the invention, the Examiner contended that the nature of the invention relies upon inhibiting PRAME with any inhibitor such as a siRNA in combination with a HDACi inhibitor in a subject such that treatment of a tumor occurs.

As for whether the specification would have been enabling as of the filing date, the Examiner considered the nature of the invention, the state of the prior art, and the level of skill in the art. The Examiner contended that the state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains.

As for the relative skill of those in the art, which the Examiner contended refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b). The Examiner contended that the state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement, and that the state of the prior art is also related to the need for working examples in the specification. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. (citing Chiron Corp. v.Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir.2004)).

The Examiner contended that a thorough review of the patent and non-patent literature indicates that the state of the art linking inhibition of PRAME and inhibition of HDACi as treatment of tumors was embryonic around the time of the instant invention. In 2005, McCarthy et al. (Nature Reviews 2005) reviews state of the art regarding the link between PRAME over- expression and tumor cell proliferation. McCarthy acknowledges the work of Applicant in showing that knock-down in expression of PRAME using a shRNA restored apoptosis in melanoma cells but cautions that the use of PRAME as a therapeutic to treat cancer in a subject requires further investigation. Furthermore, McCarthy indicates that

> treatment of cells with a HDAC inhibitor trichostatin A did not affect expression of PRAME. Thus it is clear that the state of the art post filing of the instant application questions the inhibition of PRAME as a therapeutic for treatment of tumors without further work and illustrates that all inhibitors of PRAME are not capable of reducing the expression of PRAME.

As for the amount of guidance or direction, the Examiner contended that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

As for the present application, the Examiner contended that while the level of one of ordinary skill practicing said invention would be high, the level of predictability is considered variable as evident in the prior art discussed above and is not considered to provide sufficient enablement to practice the claimed invention. At best, the prior art at the time of the instant invention invites further experimentation to find a treatment for any tumor type in a subject comprising administration of an inhibitor of PRAME along with an inhibitor of HDACi.

As for the existence of working examples, the Examiner contended that the working embodiment in the instant application illustrates A375 melanoma cells in vitro showed a decrease in proliferation after treatment with a RNAi molecule targeted to PRAME. The working embodiment in the instant application does not include experiments illustrating the administration of any inhibitor of PRAME and HDACi, let

alone a RNAi molecule and PXD101, into a subject such that treatment of a tumor type occurs. While the MPEP 2164.02 states the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970), the lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art.

The Examiner concluded that there is no guidance in the specification that would be considered enabling for the breadth of the claimed subject matter and the working embodiment not predictive of the invention as claimed. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

The Office action of January 5, 2010

The record further shows that in the January 5, 2010 Office action, the Examiner reasoned that the nature of the invention relies upon inhibiting PRAME with a RNAi in combination with any HDAC inhibitor in a subject such that treatment of a tumor occurs and contended that the instant specification does not exemplify all known HDAC inhibitors, such as nucleic acid inhibitors, antibodies or other small molecule or chemical inhibitors which are encompassed by the breadth of the claims nor does the specification exemplify or provide guidance for treatment of any tumor type with RNAi in combination with any HDAC inhibitor in a subject. As stated previously, the Examiner contended that McCarthy et al. (Nature Reviews 2005), who reviews the state of the art regarding the link between PRAME over-expression and tumor cell proliferation, acknowledges the work of Applicant in showing that knock-down in expression of PRAME using a shRNA restored apoptosis in melanoma cells in vitro but cautions that the use of PRAME as a therapeutic to treat cancer in a subject requires further investigation, and indicates that treatment of cells with a HDAC inhibitor trichostatin A

did not affect expression of PRAME. The Examiner concluded that it is clear that the state of the art questions the inhibition of PRAME as a therapeutic for treatment of tumors without further work and illustrates that all inhibitors of PRAME are not capable of reducing the expression of PRAME.

The Examiner further contended that while the instant specification does in fact show HDAC inhibitors, the specification fails to provide enablement for a method of treating all cancer types using RNAi targeted to PRAME in combination with any HDAC inhibitors known or yet to be discovered. (emphasis added). At best, the Examiner contended that the prior art at the time of the instant invention invites further experimentation to find a treatment for any tumor type in a subject comprising administration of a siRNA targeted to PRAME along with an inhibitor of HDAC.

Applicant further argued that the reference Epping et al. provided with the IDS filed 09/21/2009 provide evidence that all of the above classes of HDAC inhibitors act in the same way with respect to PRAME, but the Examiner contended that this evidence did not provide sufficient evidence of the state of the prior art at the time of filing sufficient enough to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Examiner noted that the reference, a reference by the current inventors and was published in 2007, before the earliest priority date of the current invention, does not provide evidence of the state of the art at the time of filing.

The Examiner contended that the specification does provide guidance for a method of decreasing A375 melanoma cell proliferation in vitro using a siRNA targeted to a gene encoding PRAME wherein the cells were cultured with a HDAC inhibitor PXD101. However because the claims are drawn to any HDAC inhibitor in combination with an RNAi of PRAME to treat any tumor type in a subject, the Examiner contended that there is no guidance in the specification that would be considered enabling for the breadth of the claimed subject matter and the working embodiment is not predictive of the invention as claimed. The Examiner contended that without further guidance, one of

skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Applicants' response

In order to advance prosecution, applicants have amended independent claim 1 to recite a method of treatment of a tumour which comprises comprises administering to a subject in need of treatment an effective amount of an inhibitor of PRAME, in combination with a second agent selected from the group of an inhibitor of HDAC (an HDCAi) and a retinoid, said inhibitor of PRAME being an interfering RNA (RNAi); said inhibitor of HDAC being selected from the group consisting of trichostatin A (TSA), and PXD, 101; wherein said tumour overexpresses PReferentially expressed Antigen in MElanoma (PRAME),. Applicants reserve the right to file a divisional application directed to subject matter that is not included in the amended claims.

Applicant respectfully urges that the enablement rejection is improper for the following reasons. First, the Federal Circuit has expressly rejected the contention that claims of a patent must be construed as being limited to the embodiments. See Liebel-Flarsheim, Co. v. Medrad, Inc., 358 F.3d 898, 906 (Fed. Cir. 2004) (citing ACTV, Inc. v. Walt Disney Co., 346 F.3d 1082, 1091 (Fed. Cir. 2003); Apex, Inc. v. Raritan Computer, Inc., 325 F.3d 1364, 1377 (Fed. Cir. 2003), Altiris, Inc. v. Symantec Corp., 318 F.3d 1363, 1373 (Fed. Cir. 2003), Tex. Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1204-05 (Fed. Cir. 2002); Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1327 (Fed. Cir. 2004)); and SRI Int'l v. Matsuchita Elec. Corp. of Am., 775 F.2d 1107, 1121 n. 14 (Fed. Cir. 1985) (en banc)).

Second, the Federal Circuit has held that claims should not be narrowed to the preferred embodiments unless the specification suggested the inventor intended such narrow coverage. Id. ("even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated

clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction'"); see also Lizardtech, Inc. v. Earth Resource Mapping, Inc., 433 F.3d 1373, 1377 (Fed. Cir. 2006) (citing JVW Enterprises, Inc. v. Interact Accessories, Inc., 424 F.3d 1324, 1335 (Fed. Cir. 2005) and Phillips v. AWH Corp., 415 F.3d 1303, 1323 (Fed. Cir. 2005) (en banc)). Here, the specification does not use "words or expressions of manifest exclusion or restriction" that would demonstrate a clear intention to limit claim scope to PXD101. Instead, the specification is replete with references to HDAC inhibitors (e.g., [0042]-[0049] of which PXD101 is only one example. The specification does not use "words or expressions of manifest exclusion or restriction" that would demonstrate a clear intention to limit claim scope as to the type of tumor to melanoma. Indeed, para. [0138] of the specification discloses that melanoma cells and other tumour cells that over-express PRAME are subjects that are likely to benefit most from treatment. Moreover, it discloses that PRAME expression phenocopies the PML-RARα and PLZF-RARα translocations seen in acute promyelocytic leukemia.

Third, the scope of enablement is not limited to what has been disclosed; it is that which is described in the specification plus the scope of what would be known to a person of ordinary skill in the art without undue experimentation. *See, e.g., Invitrogen Corp. v. Clontech Labs, Inc.*, 429 F.3d 1052, 1070-71 (Fed. Cir. 2005). At the time the invention was made, a skilled artisan in this field would be able to read the specification and follow the guidance of the exemplified embodiments and the knowledge in the art to make and use the claimed method. This may require some routine experimentation, but routine experimentation is not undue experimentation.

Fourth, the in vitro experiments using cell lines B16 (mouse melanoma), FM6 (a human HAGE-positive melanoma cell line), SK23 (human melanoma), A375 (human amelanotic melanoma cell line), and in vivo human melanoma xenograft model disclosed in the specification in effect constitutes a working example since those examples correlate with a disclosed or claimed method invention. See MPEP 2164.02, Each of these lines originated from actual specific melanoma tumors. While "[t]esting

for the full safety and effectiveness" of an HDACi "is more properly left to the Food and Drug Administration, (FDA),' it is well-established that "[t]itle 35 does not demand that such human testing occur within the confines of PTO proceedings." In re Brana, 51 F3d 1560 (Fed. Cir. 1995). Applicants urge that the described in vitro and in vivo results with the above-referenced cell lines are predictive for human therapy because "usefulness in patent inventions necessarily include the expectation of further research and development" [Id. at 1568].

Applicants therefore urge that the disclosure complies with the requirements of 35 U.S.C. 112 para. 1, and respectfully request that this ground for rejection be withdrawn.

Since there is no prior art that teaches or suggests the claimed invention, Applicant respectfully requests that the Examiner withdraw all objections to and rejections of the present invention.

Applicant urges that this application is now in condition for allowance and earnestly solicits early and favorable action by the Examiner. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is respectfully urged to telephone the undersigned at 973-360-7934. The undersigned also may be contacted via e-mail at lubitb@gtlaw.com.

AUTHORIZATION

The Commissioner hereby is authorized to charge any fees, including the appropriate fee for a submission of a terminal disclaimer by a small entity, which may be required, or credit any overpayment to Deposit Account 501561.

Respectfully submitted,
For Greenberg Traurig
By

Date: 6/4/10

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